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(54) COMPOSITION AND METHOD FOR THE TREATMENT  
OF MASTITIS

- (71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- Mastitis is an inflammatory condition of the mammary gland. It may affect any species, but bovine mastitis is of the greatest economic importance.
- Bovine mastitis is usually associated with one or more microorganisms such as *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Staphylococcus aureus*, *Aerobacter aerogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Clostridium perfringens*, and *Corynebacterium pyogenes* which invade the udder through the teat canal and produce inflammation of the milk-producing tissue causing the formation of scar tissue which, once formed, may cause a permanent reduction in the cow's milk production. An infection can also alter the composition, quantity, appearance and quality of the milk.
- The etiology of mastitis makes control of the problem dependent upon the critical diagnosis of the specific microbial agent involved, the correction of faulty managerial practices and the judicious use of intramammary therapy.
- The present invention provides a novel composition comprising an anti-mastitis medicament dispersed in a gelled vehicle comprising a mineral oil or a non-drying, semi-drying, or drying vegetable oil, or a mixture thereof, other than a mixture consisting of a drying and a semi-drying vegetable oil, and from 0.5 to 5% by weight of a fatty acid ester derived from a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms, and
- glycerin, propylene glycol, a mono- or dihydric alcohol of from 1 to 12 carbon atoms, or a polyethylene glycol having a molecular weight of from 200 to 6000.
- The present invention also provides a method of treating mastitis in milk-producing animals which comprises administering to the affected mammary region of the animal, by intra-mammary infusion, a composition comprising an anti-mastitis medicament dispersed in a gelled vehicle comprising a mineral oil or a non-drying, semi-drying or drying vegetable oil, or a mixture thereof, and from 0.5 to 5% by weight of a fatty acid ester derived from a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms, and glycerin, propylene glycol, a mono- or dihydric alcohol of from 1 to 12 carbon atoms, or a polyethylene glycol having a molecular weight of from 200 to 6000. By "milk producing animal", we mean any animal which has mammary glands and is capable of milk production.
- The invention will generally be described with reference to the treatment of bovine mastitis, which is of the greatest economic importance, but it will be understood that the compositions and methods of the invention are applicable to other milk-producing animals.
- The invention has been found to be particularly advantageous for the treatment of mastitis because of a surprisingly short antimastitis medicament milk-out time i.e. the amount of time required for an anti-mastitis medicament to clear the udder after the last intramammary infusion. This property of a short anti-mastitis medicament milk-out time is of importance since milk contaminated with an anti-mastitis medicament cannot be used for human consumption or marketed for cheese production.
- The nature of the vehicle, on anti-mastitis medicament milk-out times, has long been considered important in formulating mastitis

infusion compositions.

Heretofore, anti-mastitis medicaments for intramammary infusion have commonly been dispersed in an oil medium such as mineral oil or a vegetable oil containing a trivalent metallic stearate such as aluminium monostearate, e.g. a peanut oil medium containing 3% of aluminium monostearate. A disadvantage with intramammary infusion compositions containing a trivalent metallic stearate, as described above, is that the anti-mastitis medicament milk-out time for such compositions is quite long.

It is therefore a principal object of this invention to provide compositions and methods for treating animal mastitis by intramammary infusions affording short anti-mastitis medicament milk-out times.

The term "anti-mastitis medicament", as used in the specification and claims, refers to any antimicrobial effective to treat mastitis. Anti mastitis medicaments which can be utilized in the compositions of the present invention include, for example, penicillin, neomycin, novobiocin, lincomycin, dihydrostreptomycin, streptomycin, erythromycin, polymyxin, tetracycline, oxytetracycline, chlorotetracycline, clindamycin, nitrofurazone, cephalosporins, analogs and derivatives thereof, and their pharmaceutically acceptable salts. The amount of anti-mastitis medicament employed will, of course, vary depending upon the severity of the mastitis but, in general, those amounts which have heretofore been used for the treatment of mastitis are suitable.

In accordance with a specific feature of this invention, the oil of the vehicle may be any vegetable oil which is suitable for carrying an anti-mastitis medicament and which has been found fully acceptable for intramammary infusion. Vegetable oils may be generally classified as non-drying, semi-drying and drying oils. Drying vegetable oils include linseed oil and safflower oil. The drying properties of this group of oils is caused by the presence of unsaturated fatty acids in the oil. The degree of unsaturated fatty acids present can be expressed by the iodine value of the oil. Arranged according to their iodine value, the aforementioned drying vegetable oils are as follows:

Linseed oil	not less than 170
Safflower oil	140-150

The class of semi-drying vegetable oils includes the following, arranged according to their iodine value.

Soybean oil	127-138
Cottonseed oil	105-144
Sesame oil	103-122
Corn oil	109-133

The class of non-drying vegetable oils

includes the following, arranged according to their iodine value:

Olive oil	79-90
Peanut oil	84-102

As stated, vegetable oils have been found suitable for the vehicle, examples being peanut oil, sesame oil, corn oil, cottonseed oil, soybean oil, olive oil, and like vegetable oils or mixtures thereof. In a broader aspect, it is conceived that other oils may be employed, in part or in whole, for example, mineral oil. However, in such compositions, the milk-out specifications may require that the milk be completely clear of such oil in order to be available for human consumption.

The term "mineral oil" as used in the specification and claims refers to mixtures of liquid hydrocarbons known in medicine as liquid paraffin and light liquid paraffin or petroleum, preferably those of the United States or British Pharmacopoeias.

The vegetable or mineral oil is transformed to a gel before being incorporated into the compositions of the present invention. This gelling is effected by treatment of the oil with a fatty acid ester derived from a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms and glycerin, propylene glycol, mono- or dihydric alcohol of from one to twelve carbon atoms, or a polyethylene glycol having a molecular weight of from 200 to 6000. A preferred fatty acid ester of the present invention is glycerol monostearate.

The amount of glycerol monostearate or other fatty acid ester which can be used in accordance with this invention is from 0.5 to 5.0% by weight, and preferably from 1.0 to 4.0% by weight. A gel formed by gelling peanut oil with 2.0% by weight of glycerol monostearate is a preferred vehicle for the preparation of compositions of this invention.

Optionally, the vehicle of the present invention may also include a fatty acid salt i.e. a sodium, potassium or lithium salt of a saturated or unsaturated monocarboxylic acids having from twelve to twenty carbon atoms. A preferred fatty acid salt of the present invention is potassium stearate.

The amount of potassium stearate or other fatty acid salt which can be used in accordance with this invention is generally from 0.02% to 0.15% by weight. A gel formed by gelling peanut oil with 2.0% by weight of glycerol monostearate and 0.12% by weight of potassium stearate produces an eminently satisfactory vehicle for the preparation of the compositions of this invention.

To gel a mineral oil or a vegetable oil, the oil is heated to a suitable temperature which may vary somewhat with different

oils but which will generally be below 100°C. Peanut oil, for example, can be readily gelled by heating it to 60-90°C. and adding 2.0% by weight of glycerol monostearate, and then cooling to 25°C. with stirring. There is no great danger in over heating, provided decomposition of the oil is not engendered. Heated oils are gelled with fatty acid ester.

10 The following Examples illustrate the invention.

#### Example 1

One hundred grams of a composition for the treatment of mastitis is prepared from the following types and amounts of ingredients:

Procaine Penicillin G	500,000 Units
Sodium Novobiocin	1.00 gram
Glycerol monostearate	1.00 gram
Peanut oil, q.s.	100 grams

20 Heat the peanut oil to 60-90°C. and add the glycerol monostearate, cool to 25°C. with stirring. Add the sodium novobiocin and procaine penicillin G with stirring and pass the product through a colloid mill. Fill the milled product into disposable mastitis syringes in 10 gram doses.

The foregoing composition is useful for the treatment of bovine mastitis by intramammary infusion.

#### Example 2

One hundred grams of a composition for the treatment of mastitis is prepared from the following types and amounts of ingredients:

Procaine Penicillin G	1,500,000 Units
Sodium Novobiocin	1.500 gram
Glycerol monostearate	1.425 gram
Potassium stearate	0.075 gram
Peanut oil, q.s.	100 grams

40 Heat the peanut oil to 60-90°C. and add the glycerol monostearate and potassium stearate, cool to 25°C. with stirring. Add the sodium novobiocin and procaine penicillin G with stirring and pass the product through a colloid mill. Fill the milled product into disposable mastitis syringes in 10 gram doses.

The foregoing composition is useful for the treatment of bovine mastitis by intramammary infusion.

#### Example 3

One hundred grams of a composition for the treatment of mastitis is prepared from the following types and amounts of ingredients:

Lincomycin hydrochloride	2.0 grams
Glycerol monostearate	2.0 grams
Peanut, oil, q.s.	100 grams

60 Heat the peanut oil to 60-90°C. and add the glycerol monostearate, cool to 25°C. with stirring. Add the lincomycin hydrochloride with stirring and pass the product through a colloid mill. Fill the milled product into disposable mastitis syringes in 10

gram doses.

The foregoing composition is useful for the treatment of bovine mastitis by intramammary infusion.

#### Example 4

One hundred grams of a composition for the treatment of mastitis is prepared from the following types and amounts of ingredients:

Procaine Penicillin G	500,000 Units
Sodium Novobiocin	1.00 gram
Glycerol monostearate	1.00 gram
Mineral oil, q.s.	100 grams

Heat the mineral oil to 60-90°C. and add the glycerol monostearate, cool to 25°C. with stirring. Add the procaine penicillin G and sodium novobiocin with stirring and pass the product through a colloid mill. Fill the milled product into disposable mastitis syringes in 10 gram doses.

The foregoing composition is useful for the treatment of bovine mastitis by intramammary infusion.

#### WHAT WE CLAIM IS:—

1. A composition comprising an antimastitis medicament dispersed in a gelled vehicle comprising a mineral oil or a non-drying, semi-drying, or drying vegetable oil, or a mixture thereof, other than a mixture consisting of a drying and a semi-drying vegetable oil, and from 0.5 to 5% by weight of a fatty acid ester derived from a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms, and glycerin, propylene glycol, a mono- or dihydric alcohol of from 1 to 12 carbon atoms, or a polyethylene glycol having a molecular weight of from 200 to 6000.

2. A composition according to claim 1 in which the vegetable oil is peanut oil.

3. A composition according to claim 1 or claim 2 in which the fatty acid ester is glycerol monostearate.

4. A composition according to any preceding claim in which the vehicle additionally comprises from 0.02 to 0.15% by weight of a sodium, potassium or lithium salt of a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms.

5. A composition according to claim 4 in which the fatty acid salt is potassium stearate.

6. A composition according to claim 1 substantially as herein described with reference to any of the Examples.

7. A method of treating mastitis in milk-producing animals which comprises administering to the affected mammary region of the animal, by intra-mammary infusion, a composition comprising an antimastitis medicament dispersed in a gelled vehicle comprising a mineral oil or a non-drying, semi-drying or drying vegetable oil, or a mixture thereof, and from 0.5 to 5% by weight of a fatty

acid ester derived from a saturated or unsaturated monocarboxylic acid having from 12 to 20 carbon atoms, and glycerin, propylene glycol, a mono- or dihydric alcohol of 5 from 1 to 12 carbon atoms, or a polyethylene glycol having a molecular weight of from 200 to 6000.

8. A method according to claim 7 in

which the composition is a composition according to any of claims 1 to 6.

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